REMARKS

Claims 1-13, 15, 33, and 43-45 are pending in the instant application. In the June 15, 2004 Office Action, the Examiner rejected claims 1-13, 15, 33, and 43-45 under 35 U.S.C. §103(a) as allegedly being unpatentable over AT 393505 and Eibl, et al. (EP 534,445), each taken alone, for reasons already of record. Specifically, the Examiner has taken the position that the cited references teach phosphates, phosphoamines, and phosphate esters which are structurally similar to the instant claimed compounds, asserting that the difference between some of the compounds of the prior art and the claimed compounds "is that the instant claimed compounds are generically described in the prior art." In particular, the Examiner directed attention to pages 3, 4, 17, and 22-25 and Examples 13 and 14 of AT 393505. According to the Examiner, this reference also teaches phosphate esters which are structurally similar to the instant compounds, the specific example compounds differing from Applicants' claimed compounds only by a methylene group. The Examiner specifically compared Applicants' claim 1 (wherein p=8 and q=5) and the reference's Example 14 (p=8 and q=4), stating that one recites a pentyl group (q=5) where the other recites a butyl group (q=4). According to the Examiner, one such homologue does not represent an advance over the other because one of skill in the chemical art, knowing the properties of one homologue, would know what to expect of the other. The Examiner asserted that Applicants have not demonstrated in a side-by-side showing any unexpected beneficial results of the claimed compounds over the specie prepared in the cited prior art.

In response, Applicants respectfully traverse the Examiner's rejection. In the claimed compounds, the double bond in A is at a distance from O which does not appear in a naturally-occurring corresponding radical, i.e., the double bond is not at the same position as it would be in the underlying naturally-occurring alcohol or acid. As set forth throughout the specification, such modifications, achieved through a novel process, allow one to change and specifically control the physical, biochemical, and biological properties of the compounds. Such structural variations in the apolar region lead to compounds exhibiting improved antitumor activity (See page 4, lines 15-24

and page 14, lines 20-32), and further allow one to produce the compounds in industrial quantities.

In further support of Applicants' position, Applicants attach hereto data comparing alkylphosphocholines (AIPCs), having cis-double-bonds in non-naturally occurring positions of the alkyl chains (as recited in claim 1), to hexadecylphosphocoline (HePC). The attached data demonstrate particular advantages that are due to the presence of the cis-double bonds in the alkyl chains. These advantages are not seen in compounds with trans-double bonds. The important advantages include, *inter alia*, better safety and efficacy of AIPCs in comparison to HePC.

As is particularly evident in the data presented in the Table, a considerable reduction of the tumor volume is effected with the compounds of the invention when used at small doses compared to the effects seen at higher doses of HePC. Furthermore, even with a reduction of the tumor volume to <0.2%, no toxicity has been detected with the AIPC. In contrast, toxic side effects were observed with HePC, even with a smaller reduction of the tumor volume-- to < 2%. These data clearly demonstrate that the AIPCs of the present invention have surprising and unexpected properties. Accordingly, the present claims are not obvious over the art cited by the Examiner, and thus, Applicants respectfully request that the Examiner reconsider and withdraw the rejections under 35 U.S.C. §103. If the Examiner would prefer to see the attached data in the form of a Rule 132 Declaration, the Examiner is invited to telephone the Applicants' undersigned attorney, who will be pleased to submit such a Declaration for consideration.

In view of the above remarks and attached data, Applicants believe that the Examiner's rejections set forth in the June 15, 2004 Office Action have been fully overcome and that the present claims fully satisfy the patent statutes. Applicants therefore believe that the application is now in condition for allowance. The Examiner is invited to telephone the undersigned if it is deemed to expedite allowance of the application.

Respectfully submitted,

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Attachment: Comparison data
2923-123.am5.wpd

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Prof. Dr. H. Eibl

- Alkylphosphocholines in Cancer Therapy -

The Advantages of Alkylphosphocholines having a Cis-Double-Bond in non-naturally occurring Positions compared to Hexadecylphosphocholines

As shown in the table (enclosure 1) and explained in the text, alkylphosphocholines (AlPCs) with cis-double-bonds in non-naturally occurring positions of alkyl chains have different advantages over hexadecylphosphocholine (HePC). These advantages are strictly limited to the presence of cis-double bonds in the alkyl chains – they are not observed in the case of trans-double bonds.
The advantages include different important general aspects such as mode of application, range of safe application (therapeutic window) and efficacy of AlPCs in comparison to He PC.

Mode of Application

a) AlPCs with cis-double-bonds in non-naturally occurring positions of the alkyl chains can be used in all of the possible application routes. They are less hemolytic and less cytolytic than HePC.

b) HePC can only be applied using the oral route due to strong side effects. But still, the therapeutic window is narrow and the application of HePC needs careful control.

Range of Safe Application

The tolerated dosage range for the application of AlPCs is marked by the onset of antineoplastic activity, for instance tumor remission and limited by the appearance of not tolerable side effects such as nausea and vomiting. This dosage range is small for HePC with a ratio of about 2 obtained by dividing the dosage for appearance of side effects by the dosage of onset of antineoplastic activity – however it is large with a ratio from 8 to >10 in the case of AlPCs with cis-double-bonds in non-naturally occurring positions of the alkyl chain (see table).

Efficacy

The table describes the efficacy of different AlPCs with non-naturally occurring cis-double-bonds in comparison to HePC.

a) AlPCs show a strong antineoplastic activity in rat MNU-mammary carcinomas (MNU = methyl-nitroso-urea induced mammary carcinomas). Significant antineoplastic activity (tumor volume reduction from control = 100 % to < 40 %) was already observed for a dose of 21 µ mol / kg body weight / week and amounts of 256 µ mol respectively were still not toxic.

b) HePC in comparison is much less active. For significant antineoplastic activity, 170 µ mol / kg body weight / week have been required, but 575 µ mol respectively were already toxic resulting in nausea and vomiting.

Conclusion

AlPCs having cis-double bonds in non-naturally occurring positions of the alkyl chains are of advantage in cancer therapy in comparison to HePC with respect to:

a) no restrictions for application
b) much better antineoplastic efficacy
c) less toxicity
d) large range for safe application:
   The therapeutic range for HePC with 385 µ mol / 170 µ mol is small and about 2, however it is more than 10 for the AlPC described in the table with the ratio 256 µ mol / 21 µ mol.

Thus, HePC remains the first AlPC used for clinical application. However, the new molecules with cis-double bonds in the alkyl chains are the molecules to be favored in future applications.

Prof. Dr. H. Eibl

Table: AlPCs containing specific structural elements such as cis-double-bonds in non-naturally occurring positions in comparison to HePC for Cancer Therapy

MNU-Tumor[1] (Rats) Dose [2]	Reduction of Tumor Volume ml		Dose 0 = 100 %	
	HePC [3]	AlPC [4]	HePC	AlPC
0	44	52	100	100
21	ns [5]	17	--- [6]	33
42	ns	4	—	8
84	ns	1	—	2
170	15	0.2	34	0.4
256	2	< 0.1	5	< 0.2
385	1	---	2	—
575	toxic	---	toxic	—

1) MNU-tumor, methyl-nitroso-urea induced mammary carcinomas
2) weekly dose in µ mol / kg body weight
3) HePC, hexadecylphosphocholine (MW 407.58)
4) AlPC, alkylphosphocholine stands for (Z)-10-Docosenyl-1-phosphocholine (MW 489.72). Other AlPCs, for instance (Z)-12-Heneicosenyl-1-PC (MW 475.7), (Z)-16-Docosenyl-1-PC (MW 489.7), (Z)-12-Tricosenyl-1-PC (MW 503.8), (Z.Z.)-Eicosadienyl-1-PC (MW 460.4), (Z.Z.)-10.21-Docosadienyl-1-PC (MW 487.7) and (Z.Z.-10.16-Docosadienyl-1-PC (MW 487.7) behave similar and also have very strong antineoplastic activity in the rat MNU-tumor model.
5) ns, not significant
6) —, not determined